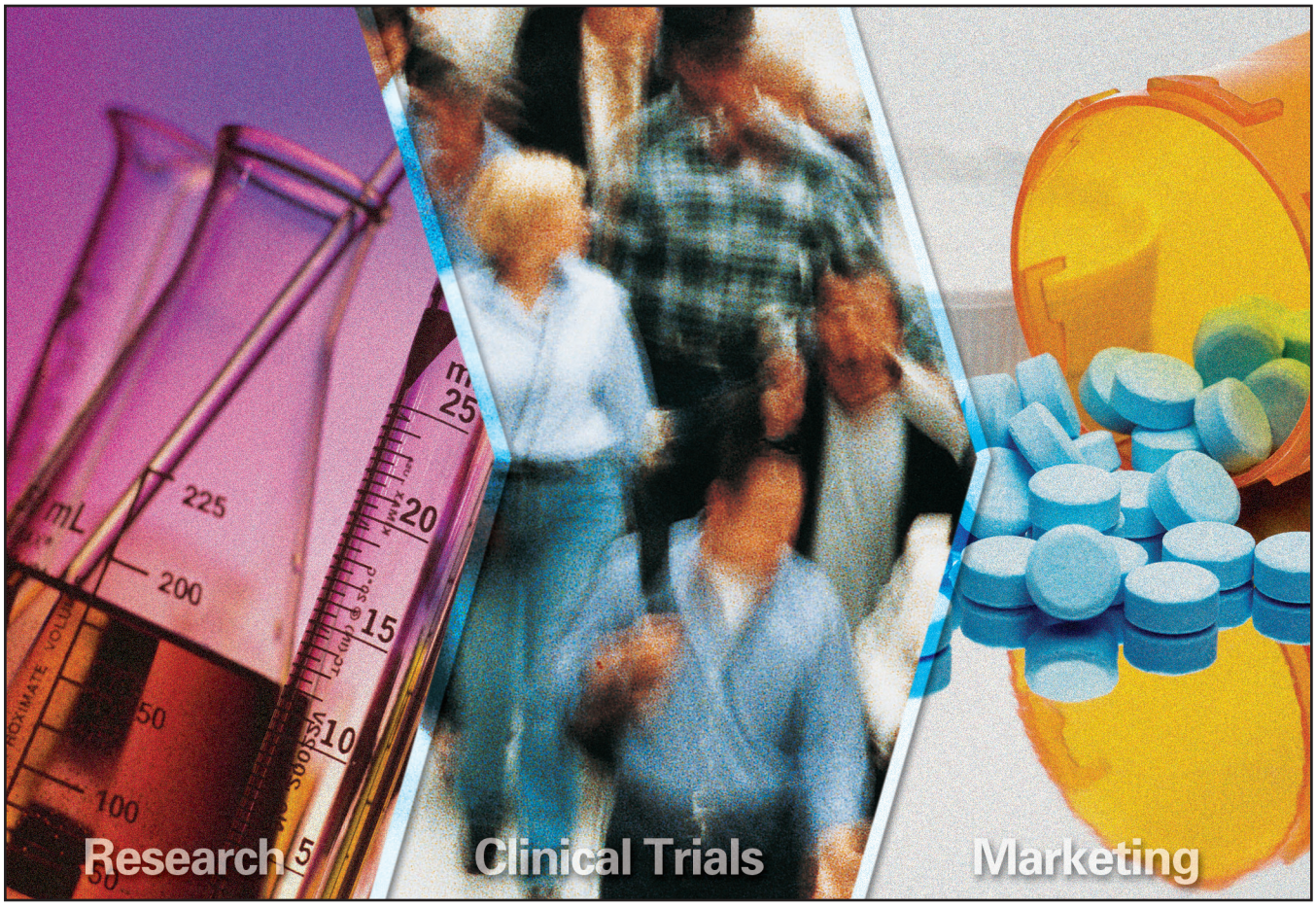

How Are Drugs Approved?
Part 3. The Stages of Drug Development

ABSTRACT

The first article of this series on the drug development process described the historical evolution of the U.S. Food and Drug Administration (FDA), and last month's article reviewed the ethical foundations of clinical research. Before a new drug is marketed, a sequence of preclinical investigations and three phases of clinical studies are conducted. This drug development process involves the FDA, pharmaceutical companies (sponsors), clinical investigators, and institutional review boards. This article further describes this aspect of the drug development process.

Before a new drug is marketed, various preclinical and clinical studies are conducted through a sequence of drug development stages. This complex and lengthy process involves the U.S. Food and Drug Administration (FDA), pharmaceutical companies (sponsors), clinical investigators, and in-

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stitutional review boards (IRBs). To provide an overview of the drug development process, the first article of this series described the historical evolution of the FDA, and last month's article reviewed the ethical foundations of clinical research. This final article focuses on the stages of drug development.

WHO IS INVOLVED IN DRUG DEVELOPMENT?

The FDA has ultimate authority and responsibility for regulating drug development and marketing. The FDA regulations are outlined in the Code of Federal Regulations (CFR), Title 21 (known as 21 CFR). The FDA establishes guidelines for conducting drug development research, establishes the qualifications for research investigators, reviews regulatory documents and research data submitted by sponsors, inspects and audits data collection from investigational sites to monitor regulatory compliance, and regulates local IRB activities. The FDA requires that clinical research be conducted according to regulatory guidelines known as Good Clinical Practices (GCP). The GCP guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical research studies (FDA, n.d.). They ensure that clinical trials are credible and that study participants are protected. The FDA also monitors the safety of approved drugs after marketing.

A sponsor initiates research investigation of a new drug by developing preclinical and clinical studies according to FDA guidelines, selecting qualified investigators to conduct the research, monitoring data collection throughout the studies, and submitting required information to the FDA. The sponsor documents financial disclosure by investigators as outlined in Part 54 of the FDA regulations (21 CFR 54). A sponsor often uses a contract research organization (CRO) specializing in the clinical and regulatory monitoring of drug studies. The CRO monitors research sites to ensure compliance with research protocols and regulatory guidelines, and it is subject to FDA inspections and audits. The sponsor is responsible for ongoing monitoring of drug safety after approval and is obligated to submit serious adverse events reports to the FDA.

An investigator actually conducts the drug research at a site. The primary responsibilities of the investigator are to ensure that study participants are recruited ethically, evaluated stringently for appropriateness, and monitored closely for their safety, and to conduct study procedures according to the protocol. The protection of human participants and informed consent are governed by FDA regulations (21 CFR 50). Investigators have the ethical and clinical responsibility to rigorously apply the inclusion and exclusion criteria when evaluating individuals for participation. Not all participants are appropriate for research; investigators must determine whether it is in the best interest of each person to participate.

Investigators are ultimately responsible for all aspects of the conduct of a study at a research site. They must adhere to GCP guidelines, assume control for the investigational drug, and maintain all regulatory documents (including correspondence with the IRB and the sponsor or CRO). The FDA requires that investigators sign a "contract" (FDA form 1572) that outlines what is expected and establishes their qualifications, but investigators typically do not correspond directly with the FDA except during an audit.

IRBs review and must approve protocols, consent forms, and any advertising or recruitment materials. The primary responsibility of the IRB is to ensure that participants' safety and well-being are protected. An IRB has the authority to approve, approve with modifications, or disapprove research studies. Studies are typically reviewed by the IRB annually, although higher risk studies may be reviewed more frequently. Although IRBs are locally constituted, they are FDA regulated, and their structure and function are outlined in 21 CFR 56. The FDA has jurisdiction to conduct audits of an IRB and can impose sanctions.

WHAT ARE THE STAGES OF DRUG DEVELOPMENT?

The drug approval process consists of various development phases (Lipsky & Sharp, 2001; Rivas-Vazquez & Mendez, 2002). Bringing a drug to market is expensive and can take up to 15 years. Not all drugs generate revenues that greatly exceed development costs, and investigational drugs are continuously scrutinized for their potential viability and profitability (Miller, 2005). For every 5,000 compounds initially evaluated, approximately one is approved.

The preclinical testing phase (drug discovery phase) involves extensive research to identify potentially therapeutic drugs and to collect pharmacology and toxicology data from labo-

ratory and animal experiments. Pharmacology data include pharmacokinetics (absorption, distribution, metabolism, and elimination) and pharmacodynamics (e.g., receptor binding, organ effects). Toxicology data include carcinogenicity, teratogenicity, and dose-dependent lethality (i.e., the dosage or concentration that kills a certain percentage of animals).

When a sponsor believes that preclinical studies justify proceeding with drug development, an Investigational New Drug (IND) application must be submitted to the FDA before research on human beings begins (FDA regulation 21 CFR 312). The IND application includes data from all preclinical studies, manufacturing information, the rationale for conducting clinical studies, the protocol that describes all aspects of the clinical phases of investigation, and information about clinical investigators. The sponsor can proceed with clinical studies unless the FDA issues a hold that requires additional data for review.

Phase I clinical testing is the first "in-human" experience during drug development. The primary purpose of a Phase I clinical trial is to establish the drug's safety and dosage in healthy volunteers. This involves administering the drug to a small number of participants (usually 20 to 80 people) across a gradually escalating dosage range, while monitoring for the development of adverse effects and collecting laboratory, pharmacokinetic, and pharmacodynamic data.

Once the drug's safety has been established from Phase I studies, Phase II testing is done to determine the drug's efficacy for a particular medical condition. Phase II clinical trials are randomized, double-blind, placebo-controlled studies with a small group of participants (usually 100 to 300 patients). European regulatory agencies often require an active control drug with established efficacy for the medical condition under investigation, if one exists, in such studies (San Miguel & Vargas, 2006). Clinical and laboratory data regarding efficacy and adverse effects are obtained at different dosages, along with additional pharmacokinetic and pharmacodynamic data.

Phase III clinical trials are randomized, double-blind, placebo-controlled studies with a larger sample of participants (usually several thousand patients). The larger sample is more varied and more representative of the general population than that in Phase II studies and allows for somewhat more generalizable results. Participants are randomized to various drug dosages to determine dosage-related efficacy and adverse effects. A broader array of clinical and laboratory data are obtained regarding the drug's efficacy, side effects, safety, drug interactions, and other pharmacological effects. These data are used to establish the minimum effective dosage and recommended dosage range for clinical use, as well as additional information for product labeling. Phase III trials are often referred to as "pivotal trials" because they provide the final critical data the FDA uses to review a drug for possible approval.

A sponsor submits a New Drug Application (NDA) to the FDA to request approval to market a drug as a treatment (indication) for a specific medical condition (FDA regulation 21 CFR 314). The FDA requires that at least two pivotal trials be conducted prior to submitting an NDA. The NDA includes information from all preclinical and clinical studies. The FDA often uses advisory panels that have expertise with the drug or medical condition to assist in reviewing an NDA (Roden & Temple, 2005). The FDA may request additional data if there are questions about safety or efficacy. An approved drug has an indication for a specific medical condition and can only be marketed for that condition. No statements can be made about potential efficacy for other conditions.

For every 5,000 compounds initially evaluated, approximately one is approved.

After FDA approval, Phase IV clinical trials (also known as postmarketing trials) are often conducted. These studies are important for expanding the knowledge base about the drug beyond the considerable data that have been acquired from Phase I to III studies (Khan, Preskorn, & Baker, 2005; Preskorn, 2002; Schultz, 2007). Phase IV studies can be required by the FDA as part of the initial approval to obtain additional information about safety or long-term effects. These studies can also be initiated by a sponsor to obtain additional drug data, such as

its efficacy, safety, or cost effectiveness compared with another proven drug for the same indication. To market an approved drug for a different indication, a new IND application must be submitted to the FDA, and the development cycle for the new indication would begin with Phase II clinical trials.

When patents for brand-name drugs expire, manufacturers can apply to the FDA to sell generic versions by submitting an abbreviated NDA. This process does not require the generic drug sponsor to repeat preclinical and clinical (Phases I to III) research studies on ingredients or dosage forms already approved for safety and efficacy. In the abbreviated NDA, the sponsor must demonstrate that a generic drug:

- Contains the same active ingredients as the brand-name drug (although inactive ingredients may vary).
- Be identical in strength, dosage form, and route of administration.
- Have the same use indications.
- Be bioequivalent.
- Meets the same batch requirements for identity, strength, purity, and quality.
- Be manufactured according to the same FDA Good Manufacturing Practice regulations.

Drugs initially approved for children go through the same development stages described above. Most drugs are initially approved for adults, but they can be prescribed by physicians for labeled and off-label uses, including for children. Extrapolating adult data to children has been questioned, leading to FDA regulations regarding studies in pediatric populations that are covered by the Best Pharmaceuticals for Children Act of 2002 and the Pediatric Research Equity Act of 2003 (Hirschfeld, 2004; Sharfstein, North, & Serwint, 2007). As an incentive, the FDA grants a 6-month extension of marketing exclusivity to sponsors who conduct pediatric studies.

Even if a sponsor is not interested in marketing a drug in children, the FDA can mandate that pediatric studies be conducted if the drug represents a potential therapeutic advance or if widespread use of the drug is anticipated. Such studies provide data for "pediatric labeling" of a drug. This means that positive and negative information regarding pediatric use is included in the package insert, regardless of whether the drug is approved for children. Such studies can also lead to approval for a "pediatric indication," meaning that the drug is safe and effective in children.

CONCLUSION

Drug therapy has a central role in health care. Occasional problems with particular drugs often lead to criticisms of the drug approval process from clinicians, researchers, and the public. Such criticisms should always warrant attention, and they sometimes lead to meaningful changes (Wood, 2006). Nurses should understand and appreciate the scientific, regulatory, and ethical complexity of the drug development process required to bring a drug to market.

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